CLAIMS

1. A method for obtaining a cell which directs constitutive hypermutation of a target nucleic acid sequence within the cell, comprising screening a cell population for ongoing target sequence diversification and selecting a cell in the cell population in which the rate of mutation of the target sequence exceeds the rate of mutations in non-target sequences in the cell by a factor of 100 or more.

2. The method according to claim 1, wherein the cell population comprises lymphoid cells.

3. The method according to claim 2, wherein the cell population comprises is immunoglobulin-expressing cells.

4. The method according to claim 1, wherein the cell expresses a gene product encoded by the target nucleic acid sequence; and wherein screening comprises selecting for a change in the expression of the gene product.

5. The method according to claim 1, wherein the change is a loss of expression of the gene product.

6. The method according to claim 4, wherein the cell expresses the gene product on its surface.

7. The method according to claim 1, wherein the cell is from a cell line generated from a cell which hypermutates *in vivo*.

8. A method according to claim 7, wherein the cell is from a cell line selected from the group consisting of a Burkitt lymphoma cell line, a follicular lymphoma cell line, and a diffuse large cell lymphoma cell line.

9. The method according to claim 1, further comprising the steps of isolating one or more of selected cells and comparing the rate of accumulation of mutations in the target sequence in the one or more cells with the rate of mutation of non-target sequences.

10. The method according to claim 1, wherein the target sequence is an immunoglobulin V-gene sequence.

11. The method according to claim 5, wherein the gene product is an immunoglobulin.

12. The method according to claim 1, wherein mutation rates are determined by sequencing the target sequence in each of a plurality of cells from the cell population

13. The method according to claim 5, wherein the cells are contacted with an antibody which specifically binds to the gene product to identify one or more cells which do not bind to the antibody.

14. The method according to claim 1, wherein the cells are exposed to a mutagen.

15. The method according to claim 1, wherein the cells express a sequence-modifying gene product.

16. The method according to claim 1, wherein the cells comprise one or more mutated sequences providing the cells with a higher rate of mutation than cells without the one or more mutated sequences.

17. The method according to claim 16, wherein the rate of mutation is at least two-fold higher in the cells comprising the one or more mutated sequences than in the cells without the one or more mutated sequences.

18. The method according to claim 17, wherein the rate of mutation is at least ten-fold higher.

19. The method according to claim 16, wherein the one or more mutated sequences are genetically engineered into the cells.

20. The method according to claim 16, wherein the one or more mutated sequences comprises one or more mutated DNA repair genes.

21. The method according to claim 16, wherein the cells comprising the one or more mutated sequences express at least 10% less of one or more DNA repair proteins than cells without the one or more mutated sequences.

22. The method according to claim 20, wherein the one or more DNA repair genes are selected from the group consisting of Rad51, Rad 51 analogues, Rad51 paralogues, and combinations thereof.

23. The method according to claim 20, wherein the DNA repair genes are selected from the group consisting of Rad51b, Rad51c, and analogues, paralogues, and combinations thereof.

24. A method for preparing a mutated form of a gene product, comprising the steps of:

a) expressing a nucleic acid encoding the gene product, the nucleic acid operably linked to a hypermutation control sequence, in a population of constitutively hypermutating cells in which the rate of mutation of nucleic acids linked to the control sequence exceeds the rate of mutations in sequences not linked to the control sequence by a factor of 100 or more; and

b) identifying a cell or cells within the population of cells which express a mutated form of the gene product.

25. The method according to claim 24, further comprising

c) establishing one or more clonal populations of cells from the cell or cells identified in step (b), and selecting from the clonal populations a cell or cells which expresses the mutated form of the gene product.

26. The method according to claim 24, wherein the cell or cells constitutively hypermutate an endogenous V gene locus.

27. The method according to claim 24, wherein the mutated form of the gene product binds to a biomolecule to which the non-mutated form of the gene product does not bind.

28. The method according to claim 24, wherein the mutated form of the gene product is unable to bind to a biomolecule under conditions in which the non-mutated form of the gene product binds to the biomolecule.

29. The method according to claim 24, wherein the mutated form of the gene product comprises an at least two-fold greater ability to bind to a biomolecule to which the non-mutated form of the gene product binds.

30. The method according to claim 24, wherein the mutated form of the gene product comprises an at least two-fold lower ability to bind to a biomolecule to which the non-mutated form of the gene product binds.

31. The method according to claim 24, wherein the gene product is an enzyme.

32. The method according to claim 24, wherein the gene product performs a catalytic activity in the presence of a substrate and wherein the catalytic activity of the mutated gene product is increased at least two-fold compared to the catalytic activity of the non-mutated gene product.

33. The method according to claim 24, wherein the gene product performs a catalytic activity in the presence of a substrate and wherein the catalytic activity of the mutated gene product is decreased at least two-fold compared to the catalytic activity of the non-mutated gene product.

34. The method according to claim 24, wherein the hypermutation control sequence comprises a sequence occurring 3' of a J gene cluster, said sequence comprising the Jκ-Cκ intron sequence, Cκ, and the E3' enhancer element, and wherein said Jκ-Cκ intron sequence comprises the Ei/MAR enhancer element sequence.

35. The method according to claim 34, wherein the sequence 3' of Cκ and 5' of E3' comprises a 7.34 kb deletion.

36. The method according to claim 24, wherein the nucleic acid encoding the gene product is an exogenous sequence operably linked to an endogenous control sequence.

37. The method according to claim 36, wherein the exogenous gene is operably linked to the Jκ intron.

38. The method according to claim 36, wherein the exogenous sequence is a heterologous coding sequence not naturally found in the cell or cells.

39. The method according to claim 36, wherein an endogenous V region coding sequence is replaced by a heterologous coding sequence not naturally found in the cell or cells' genomes.

40. The method according to claim 24, wherein the gene product is an immunoglobulin.

41. The method according to claim 24, wherein the gene product is a DNA binding protein.

42. A cell for directing constitutive hypermutation of a target gene, wherein the cell is a genetically manipulated chicken bursal lymphoma cell in which the rate of nucleic acid mutation at a target sequence in the cell operably linked to a hypermutation control sequence for directing mutations to the target sequence exceeds the rate of mutations in non-target nucleic acids by a factor of 100 or more.

43. The cell according to claim 42, wherein the chicken bursal lymphoma cell is a DT40 cell.

44. A cell selected from the group consisting of Δ xrcc2 DT40 and Δ xrcc3 DT40.